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Via Hand Delivery

Food and Drug Administration
Dockets Management Branch
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Citizen Petition to Request Uniform Professional Labeling for Promethazine HCL Formulations: Request for updated information to be added to the **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION** Sections of the Professional Labeling for Promethazine Hydrochloride Syrup, USP.

Dear Sir/Madam,

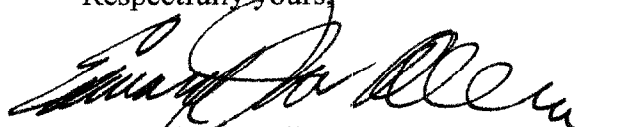
Pursuant to 21 CFR 10.30, the enclosed Citizen Petition has been prepared to request the amplification of the current labeling for marketed formulations of Promethazine Hydrochloride Syrup, USP to properly reflect the potential for serious respiratory depression in pediatric patients. The requested labeling will provide the information already included in the labeling for Promethazine Tablets and Suppositories. All three formulations are marketed for the same indications in pediatric patients and, as such, should reflect uniform labeling relating to life threatening events.

The labeling for Promethazine Tablets and Suppositories (Phenergan®, Wyeth) was amplified in 2004 to specifically contraindicate the use of these products in children two years of age and younger. The labeling was also amplified to provide new respiratory related warnings relating to their use in all children. The new labeling specifically warns of the potential for fatal respiratory events in all children, including those two years of age and older. To date, these critical labeling changes have not been extended to the syrup product although this formulation is widely used in the younger pediatric populations and in babies.

The enclosed submission includes three copies of the Citizen Petition.

Please contact the undersigned if you have any questions or require additional information.

Respectfully yours,


Edward John Allera

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2005P-0173

Enclosures

CITIZEN PETITION

Edward J. Allera and Buchanan Ingersoll submit this petition to request action by the Food and Drug Administration (FDA) relating to the drug product, Promethazine Hydrochloride Syrup, USP, marketed by Morton Grove Pharmaceuticals, Inc. and other manufacturers of this product. The petitioners request that FDA require all manufacturers of Promethazine Hydrochloride Syrup, USP to adopt the labeling changes already implemented for Promethazine HCL Tablets and Suppositories and fully warn prescribers and health care professionals of the potential for fatal respiratory depression in pediatric patients. The proposed labeling additions include the addition of a Contraindication for use in pediatric patients less than two years of age, the addition of a Black Box Warning concerning its use in all pediatric patients, and the addition of supplementary information relating to respiratory events in the Precautions, Adverse Reactions, and Dosage and Administration sections. The new labeling clearly warns of the potential for fatal respiratory events in infants and children.

Given the critical nature of the requested information, this Petition also requests the dissemination of "Dear Doctor", "Dear Healthcare Professional" and "Dear Pharmacist" letters to advise the medical community of these critical labeling changes.

This petition is submitted pursuant to 21 CFR 10.35, and relating to 21 CFR 201.5, 201.128, and Sections 201(n), 502(a), 502(f)(1) and 505 of the Federal Food, Drug and Cosmetic Act.

I. Introduction and Action Requested

Multiple manufacturers of Promethazine Hydrochloride Syrup, USP are noted in FDA's publication entitled "Approved Drug Products with Therapeutic Equivalence Equations (Orange Book)". The current Edition lists Morton Grove Pharmaceuticals as the referenced listed drug product, even though this formulation was introduced to the marketplace as a generic equivalent to Wyeth's Phenergan® brand of Promethazine Hydrochloride Syrup. Wyeth subsequently discontinued the marketing of Phenergan® Syrup and the Morton Grove formulation became the referenced listed drug. Wyeth continues to manufacture and market Promethazine Hydrochloride Tablets and Suppositories under the Phenergan® trade name. In 2004, based on a request from the FDA, Wyeth revised its labeling to include critical information relating to the risks for fatal respiratory depression in pediatric patients.

A review of the currently available labeling for the Wyeth and Morton Grove Promethazine confirmed that the following indications are provided in both:

Perennial and seasonal allergic rhinitis.

Vasomotor rhinitis.

Allergic conjunctivitis due to inhalant allergens and foods.

Mild, uncomplicated allergic skin manifestations of urticaria and angioedema.

Dermographism.

Anaphylactic reactions, as adjunctive therapy to epinephrine and other standard measures, after the acute manifestations have been controlled.

Preoperative, postoperative, or obstetric sedation.

Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.

Therapy adjunctive to meperidine or other analgesics for control of post-operative pain.

Sedation in both children and adults, as well as relief of apprehension and production of light sleep from which the patient can be easily aroused.

Active and prophylactic treatment of motion sickness.

Antiemetic therapy in postoperative patients.

The Wyeth and Morton Grove inserts also provide for use in children and adults. However, the Wyeth labeling specifically contraindicates use of its products in

children under two years of age. The Wyeth labeling also provides additional warnings and other information relating to respiratory related events including fatalities in all children.

The Morton Grove labeling clearly does not fully express the potential danger of Promethazine in the pediatric populations and must be amplified immediately. The following pages provide side by side overviews of the relevant sections in the tablet and syrup labeling and illustrate the serious limitations in the latter.

**Comparison of Relevant Sections of the Professional Inserts
(see Attachments I and II)**

<u>Wyeth</u>		<u>Morton Grove</u>
Phenergan® (promethazine HCL) Tablets and Suppositories		Promethazine HCL Syrup, U.S.P. (obtained on 4-6-05)
	<u>CONTRAINDICATIONS</u>	
Phenergan Tablets and Suppositories are contraindicated for use in pediatric patients less than two years of age.		This information is not included.
	<u>WARNINGS</u>	
<p>PHENERGAN SHOULD NOT BE USED IN PEDIATRIC PATIENTS LESS THAN 2 YEARS OF AGE BECAUSE OF THE POTENTIAL FOR FATAL RESPIRATORY DEPRESSION. POSTMARKETING CASES OF RESPIRATORY DEPRESSION, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH USE OF PHENERGAN IN PEDIATRIC PATIENTS LESS THAN 2 YEARS OF AGE. A WIDE RANGE OF WEIGHT-BASED DOSES OF PHENERGAN HAVE RESULTED IN RESPIRATORY DEPRESSION IN THESE PATIENTS.</p> <p>CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PHENERGAN TO PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER. IT IS RECOMMENDED THAT THE LOWEST EFFECTIVE DOSE OF PHENERGAN BE USED IN PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER AND CONCOMITANT ADMINISTRATION OF OTHER DRUGS WITH RESPIRATORY DEPRESSANT EFFECTS BE AVOIDED.</p>		Black Box and its information are not included.

Use in Pediatric Patients	<u>WARNINGS</u>	Use in Pediatric Patients
<p>PHENERGAN TABLETS AND SUPPOSITORIES ARE CONTRAINDICATED FOR USE IN PEDIATRIC PATIENTS LESS THAN TWO YEARS OF AGE.</p> <p>CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PHENERGAN TABLETS AND SUPPOSITORIES TO PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER BECAUSE OF THE POTENTIAL FOR FATAL RESPIRATORY DEPRESSION. RESPIRATORY DEPRESSION AND APNEA, SOMETIMES ASSOCIATED WITH DEATH, ARE STRONGLY ASSOCIATED WITH PROMETHAZINE PRODUCTS AND ARE NOT DIRECTLY RELATED TO INDIVIDUALIZED WEIGHT-BASED DOSING, WHICH MIGHT OTHERWISE PERMIT SAFE ADMINISTRATION. CONCOMITANT ADMINISTRATION OF PROMETHAZINE PRODUCTS WITH OTHER RESPIRATORY DEPRESSANTS HAS AN ASSOCIATION WITH RESPIRATORY DEPRESSION, AND SOMETIMES DEATH, IN PEDIATRIC PATIENTS.</p> <p>ANTIEMETICS ARE NOT RECOMMENDED FOR TREATMENT OF UNCOMPLICATED VOMITING IN PEDIATRIC PATIENTS, AND THEIR USE SHOULD BE LIMITED TO PROLONGED VOMITING OF KNOWN ETIOLOGY. THE EXTRAPYRAMIDAL SYMPTOMS WHICH CAN OCCUR SECONDARY TO PHENERGAN TABLETS AND SUPPOSITORIES ADMINISTRATION MAY BE CONFUSED WITH THE CNS SIGNS OF UNDIAGNOSED PRIMARY DISEASE, e.g. ENCEPHALOPATHY OR REYE'S SYNDROME. THE USE OF PHENERGAN TABLETS AND SUPPOSITORIES SHOULD BE AVOIDED IN PEDIATRIC PATIENTS</p>		<p>This information is not included.</p>

WHOSE SIGNS AND SYMPTOMS MAY SUGGEST REYE'S SYNDROME OR OTHER HEPATIC DISEASES.		
	<u>WARNINGS</u>	
Excessively large doses of antihistamines, including Phenergan Tablets and Suppositories, in pediatric patients may cause sudden death (see <u>OVERDOSAGE</u>). Hallucinations and convulsions have occurred with therapeutic doses and overdoses of Phenergan in pediatric patients. In pediatric patients who are acutely ill associated with dehydration, there is an increased susceptibility to dystonias with the use of promethazine HCl.		This information is not included.
	<u>PRECAUTIONS</u>	
Pediatric Use		PEDIATRIC USE
PHENERGAN TABLETS AND SUPPOSITORIES ARE CONTRAINDICATED FOR USE IN PEDIATRIC PATIENTS LESS THAN TWO YEARS OF AGE (see <u>WARNINGS -- Black Box Warning</u> and <u>Use in Pediatric Patients</u>).		This product should not be used in pediatric patients under 2 years of age because safety for such use has not been established.
Phenergan Tablets and Suppositories should be used with caution in pediatric patients 2 years of age and older (see <u>WARNINGS -- Use in Pediatric Patients</u>).		
	<u>ADVERSE REACTIONS</u>	
Respiratory -- Asthma, nasal stuffiness, respiratory depression (potentially fatal) and apnea (potentially fatal). (See <u>WARNINGS- Respiratory Depression</u> .)		This section is not included.

	<u>DOSAGE AND ADMINISTRATION</u>	
Phenergan Tablets and Phenergan Rectal Suppositories are contraindicated for children under 2 years of age (see <u>WARNINGS-Black Box Warning</u> and <u>Use in Pediatric Patients</u>).		This section is not included.
Pre-and Postoperative Use		PRE-AND POSTOPERATIVE USE
Phenergan Tablets and Phenergan Rectal Suppositories are contraindicated for children under 2 years of age.		Promethazine Syrup Plain is not recommended for children under 2 years of age.

II. Statement of Factual Grounds

Wyeth is the innovator for Promethazine HCL products. Wyeth has discontinued its marketing of Phenergan® Syrup, but continues to manufacture and market Phenergan® Tablets and Suppositories. Phenergan® is the Reference Listed Drugs for the tablet and suppository dosage forms in the FDA "Orange Book".

In December 2004, Wyeth revised its Phenergan® labeling to include additional Contraindications, Warnings and other labeling information concerning the risk of fatal respiratory depression in pediatric patients. Wyeth also disseminated "Dear Health Care Professional" letters announcing these changes. (Attachment I).

There are multiple FDA approved generic formulations of the Promethazine HCL Syrup. Among these are the products approved for Morton Grove. These formulations currently serve as the Referenced Listed Drugs for other syrup formulations.

Specimens of the professional labeling now employed by Morton Grove for Promethazine HCL Syrups do not include the new information provided with the Phenergan Tablets and Suppositories. In fact, as noted with the attached insert obtained in April, 2005, the use of Promethazine is still not contraindicated in younger children. Moreover, this labeling fails to provide critically important information describing Promethazine related respiratory failures in children of all ages. (Attachment II).

The Petitioners believe these labeling changes are necessary and must be immediately implemented with all products. Pharmacokinetics studies have indicated that the tablet, syrup and suppository dosage forms are associated with similar extents of absorption (see Strenkoski – Nix, L.C. et al., 2000 American Journal Health System Pharmacology, 57(16) 1499-1505; S. Starchansky et al., 1984, American Journal Pharmacy Science; 76(6) 441-445; R. Zaman et al, 1986, Biopharm. Drug Dispos. 7(3) 281-291; T.L. Schwinghammer et al., 1984 5(2) 185 - 194). As such, the safety and efficacy of these formulations would be considered to be equivalent and require equally informative labeling. Certainly, there are no available data to suggest that the syrup product is safer than the Wyeth Tablets and Suppositories. Moreover, the syrup product would be expected to be employed as a suitable dosage form for all children, including the younger children and babies who are not yet able to accept solid dosage forms. Unfortunately, these patients are the ones most vulnerable to the respiratory failures observed with the Promethazine product.

The spontaneous adverse event reports submitted to the FDA's Adverse Event Reporting System have been reviewed for Promethazine products. Multiple childhood fatalities, secondary to respiratory failures, were found and Promethazine was considered the primary suspect agent for many of these. Clearly, the labeling for all formulations must provide the necessary information to ensure their safe use and to avoid these adverse events. The existing syrup labeling, with its less severe

warnings, could suggest that this formulation is associated with less serious adverse events. This could lead health care providers to preferentially choose this product over tablets or suppositories.

III. Environmental Impact Statement

The petitioners believe that the actions requested in this Petition provide no significant environmental impact. The requested actions will not introduce any substance into the environment and are categorically excluded pursuant to 21 CFR 25.30.

IV. Economic Impact Statement

This information is only to be submitted when requested by the Commissioner following a review of this Petition.

V. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies and that it includes representative data and information known to the Petitioners which are unfavorable to the Petition.

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Ed,
Please sign.